



Patent  
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## INTRAVENOUS FORMULATION OF RIFALAZIL AND METHODS OF USE THEREOF

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### Background of the Invention

The present invention features methods of treating bacterial infections.

In the last decade, the frequency and spectrum of antimicrobial-resistant  
10 infections has increased. Certain infections that are essentially untreatable are  
reaching epidemic proportions in both the developing world and institutional  
settings in the developed world. Antimicrobial resistance is manifested in  
increased morbidity, mortality, and health-care costs. *Staphylococcus aureus* is a  
significant cause of nosocomial and community acquired infections, especially skin  
15 and soft tissue infection, including surgical wound infection, nosocomial  
pneumonia, and bloodstream infection (see, for example, Panlilio et al., *Infect.  
Cont. Hosp. Epidemiol.* 13: 582-586 (1992)). Other pathogens commonly  
associated with serious infections include, but are not limited to, *Staphylococcus*  
*spp.*, *Streptococcus spp.*, *Enterococcus spp.*, and *Enterobacter spp.* There exists a  
20 need to provide alternative and improved agents for the treatment of bacterial  
infections particularly for the treatment of infections caused by resistant strains of  
bacteria such as penicillin-resistant, methicillin-resistant (e.g., methicillin-resistant  
*Staphylococcus aureus*), quinolone-resistant (e.g., quinolone-resistant  
*Streptococcus pneumoniae*), macrolide-resistant (e.g., macrolide-resistant  
25 *Streptococcus pyogenes*), and/or vancomycin-resistant (e.g., vancomycin-resistant  
enterococci) strains (see, for example, Swartz M. N., *N. Engl. J. Med.* 346:722  
(2002); Davidson et al., *N. Engl. J. Med.* 346:747 (2002); and Huovinen P., *N.  
Engl. J. Med.* 346:1243 (2002)). A considerable amount of effort has been

devoted to developing antibacterial (bacteriostatic and/or bactericidal) agents with activity against these and other microorganisms.

For the treatment of many nosocomial and serious community acquired infections, it is often desirable to administer antibacterial agents parenterally, because of the lack of predictability in the bioavailability of drugs orally administered to diseased individuals. Intravenous administration is preferred for the treatment of life-threatening infections, for patients with severe illness, for persistent infections, and for prophylaxis against postoperative infections in patients undergoing surgical procedures.

One agent that may be capable of treating a wide variety of infections is rifalazil. Rifalazil is described in the U.S. Pat. No. 4,983,602, where its antibacterial activity is disclosed.

### Summary of the Invention

We have discovered methods of formulating rifalazil for intravenous administration, compositions thereof, and methods of treating disease by administering rifalazil intravenously.

In one aspect, the invention features an aqueous solution of rifalazil suitable for intravenous administration to a human, wherein the solution has a rifalazil concentration of between 20 and 10,000  $\mu\text{g/mL}$ . Desirably, the solution has a rifalazil concentration of between 20 and 5,000, 50 and 3,000, 50 and 2,000, or 50 and 500  $\mu\text{g/mL}$ .

In one embodiment of the above aspect, the only antimicrobial constituent of the aqueous solution is rifalazil.

Particular excipients for use in the preparation of rifalazil solutions include those selected from the group consisting of polyethoxylated fatty acids, PEG-fatty acid diesters, PEG-fatty acid mono-ester and di-ester mixtures, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products,

polyglycerized fatty acids, propylene glycol fatty acid esters, mixtures of propylene glycol esters and glycerol esters, mono- and diglycerides, sterol and sterol derivatives, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, sugar esters, polyethylene glycol alkyl phenols,  
5 polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters, lower alcohol fatty acid esters, and ionic surfactants.

Solutions of rifalazil may include one or more excipients, for example, selected from the group consisting of sodium lauryl sulfate, polyoxyl-40 stearate, PEG-3 castor oil, PEG-5, 9, and 16 castor oil, PEG-20 castor oil, PEG-23 castor  
10 oil, PEG-30 castor oil, PEG-35 castor oil, PEG-38 castor oil, PEG-40 castor oil, PEG-50 castor oil, PEG-60 castor oil, PEG-100 castor oil, PEG-200 castor oil, PEG-5 hydrogenated castor oil, PEG-7 hydrogenated castor oil, PEG-10 hydrogenated castor oil, PEG-20 hydrogenated castor oil, PEG-25 hydrogenated castor oil, PEG-30 hydrogenated castor oil, PEG-40 hydrogenated castor oil, PEG-  
15 45 hydrogenated castor oil, PEG-50 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-80 hydrogenated castor oil, and PEG-100 hydrogenated castor oil.

In another aspect, the invention features a method of treating disease in a human including the intravenous administration to a human of a solution including  
20 rifalazil in amounts effective to treat disease, wherein the solution is suitable for administration to a human.

The methods of the present invention can be used to treat, for example, respiratory tract infections, acute bacterial otitis media, bacterial pneumonia, urinary tract infections, complicated infections, noncomplicated infections,  
25 pyelonephritis, intra-abdominal infections, deep-seated abscesses, bacterial sepsis, skin and skin structure infections, soft tissue infections, bone and joint infections, central nervous system infections, bacteremia, wound infections, peritonitis, meningitis, infections after burn, urogenital tract infections, gastro-intestinal tract

infections, pelvic inflammatory disease, endocarditis, and other intravascular infections.

The methods of the present invention can also be used to treat diseases associated with bacterial infection. For example, bacterial infections can produce  
5 inflammation resulting in the pathogenesis of atherosclerosis, multiple sclerosis, rheumatoid arthritis, diabetes, Alzheimer's disease, asthma, cirrhosis of the liver, psoriasis, meningitis, cystic fibrosis, cancer, and osteoporosis. Accordingly, the present invention features a method of treating the diseases associated with bacterial infection listed above, among others, by administering rifalazil  
10 intravenously.

The preoperative intravenous administration of rifalazil can reduce or eliminate the incidence of postoperative infections in patients undergoing surgical procedures. Accordingly, the methods of the present invention are useful for prophylaxis against infections resulting from surgical procedures and implantation  
15 of prosthetic devices.

The methods of the present invention can be used to treat or prevent infections by bacteria from a variety of genera, such as *Escherichia spp.*, *Enterobacter spp.*, *Enterobacteriaceae spp.*, *Klebsiella spp.*, *Serratia spp.*, *Pseudomonas spp.*, *Acinetobacter spp.*, *Bacillus spp.*, *Micrococcus spp.*,  
20 *Arthrobacter spp.*, *Peptostreptococcus spp.*, *Staphylococcus spp.*, *Enterococcus spp.*, *Streptococcus spp.*, *Haemophilus spp.*, *Neisseria spp.*, *Bacteroides spp.*, *Citrobacter spp.*, *Branhamella spp.*, *Salmonella spp.*, *Shigella spp.*, *Proteus spp.*, *Clostridium spp.*, *Erysipelothrix spp.*, *Listeria spp.*, *Pasteurella spp.*, *Streptobacillus spp.*, *Spirillum spp.*, *Fusospirocheta spp.*, *Treponema spp.*,  
25 *Borrelia spp.*, *Actinomycetes spp.*, *Mycoplasma spp.*, *Chlamydia spp.*, *Rickettsia spp.*, *Spirochaeta spp.*, *Legionella spp.*, *Mycobacteria spp.*, *Ureaplasma spp.*, *Streptomyces spp.*, and *Trichomoras spp.* Accordingly, the invention features a

method of treating infections by the bacteria belonging to the genera above,  
among others.

In another aspect, the invention features a method of treating a non-  
mycobacterial infection by Gram-positive bacteria in a human by administering  
5 rifalazil to the human in amounts effective to treat the infection.

The Gram-positive bacterial infections to be treated include infections by,  
*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*,  
*Enterococcus faecium*, *Clostridium perfringens*, *Streptococcus pyogenes*,  
*Streptococcus pneumoniae*, other *Streptococcus ssp.*, and other *Clostridium spp.*

10 In another aspect, the invention features a method of treating an infection  
by multi-drug resistant bacteria in a human by administering rifalazil to the human  
in amounts effective to treat the infection.

Resistant strains of bacteria include penicillin-resistant, methicillin-  
resistant, quinolone-resistant, macrolide-resistant, and/or vancomycin-resistant  
15 bacterial strains.

The multi-drug resistant bacterial infections to be treated using the methods  
of the present invention include infections by penicillin-, methicillin-, macrolide-,  
vancomycin-, and/or quinolone-resistant *Streptococcus pneumoniae*; penicillin-,  
methicillin-, macrolide-, vancomycin-, and/or quinolone-resistant *Staphylococcus*  
20 *aureus*; penicillin-, methicillin-, macrolide-, vancomycin-, and/or quinolone-  
resistant *Streptococcus pyogenes*; and penicillin-, methicillin-, macrolide-,  
vancomycin-, and/or quinolone-resistant enterococci.

In any of the above methods, rifalazil is desirably administered  
intravenously. The intravenously administered solution can consist of rifalazil,  
25 water, and one or more pharmaceutically acceptable excipients.

In any of the above methods, rifalazil may be administered as a  
monotherapy, e.g., where rifalazil is the only antimicrobial agent administered to  
the patient.

In any of the above methods, rifalazil is optionally administered in combination or in parallel with a second antibiotic.

The second antibiotic can be selected from the group consisting of aminoglycosides, amphenicols, ansamycins,  $\beta$ -Lactams, carbapenems, 5 cephalosporins, cephamycins, lincosamides, macrolides, polypeptides, tetracyclines, 2,4-Diaminopyrimidines, nitrofurans, quinolones, sulfonamides, lipopeptides, oxazolidones, ketolides and sulfones.

Desirable second antibiotics to be administered in combination or in parallel with rifalazil include amikacin, gentamicin, kanamycin, azithromycin, 10 tetracycline, vancomycin, and teicoplanin.

Rifalazil can be administered by intravenous infusion, wherein between 2 and 50 mg of rifalazil is administered over a period of 4 to 24 hours. Desirably, between 4 and 40 mg, 4 and 30 mg, or 8 and 25 mg of rifalazil is administered over a period of 4 to 24 hours, 8 to 24 hours, or 15 to 24 hours. Up to 2, 4, 6, 8, 15 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, or 50 mg of rifalazil is administered by intravenous infusion over a 2, 4, 5, 6, 7, 8, 9, 10, 12, 14, 20, 24, 48, or 72 hour period.

Rifalazil can be administered by intravenous bolus of between 2 and 25 mg of rifalazil over a 10 to 60 minute period followed by a slow infusion of 0.1 to 2 20 mg, 0.5 to 2 mg, 0.5 to 1.5 mg, or 1 to 2 mg, per hour for up to 24 hours.

The intravenous administration of rifalazil may be repeated daily or every other day, for a period of two to fourteen days. Desirably, the intravenous administration can be repeated every third day for a period of three to fifteen days.

In another aspect, the invention features a method of treating disease in a 25 human by intravenously administering rifalazil at a rate that maintains a plasma concentration of rifalazil of between 4 and 80, 6 and 50, or 10 and 50 ng/mL for a period greater than 5, 8, 12, or 24 hours.

Desirably, rifalazil is administered in a dosing schedule that maintains a plasma concentration of rifalazil of between 4 and 50, 6 and 60, or 6 and 40 ng/mL for a period greater than 24 hours.

In another aspect, the invention features a pharmaceutical formulation for  
5 intravenous administration including rifalazil. The formulation includes an aqueous solution of rifalazil and is packaged with a label or package insert providing instructions for the use of the formulation wherein the instructions describe an intravenous dosing schedule.

As used herein, the term "treating" refers to administering a pharmaceutical  
10 composition for prophylactic and/or therapeutic purposes. To "prevent disease" refers to prophylactic treatment of a patient who is not yet ill, but who is susceptible to, or otherwise at risk of, a particular disease. To "treat disease" or use for "therapeutic treatment" refers to administering treatment to a patient already suffering from a disease to improve or stabilize the patient's condition.  
15 Thus, in the claims and embodiments, treating is the administration to a mammal either for therapeutic or prophylactic purposes.

The term "administration" or "administering" refers to a method of giving a dosage of a pharmaceutical composition to a mammal, where the method is, for example, topical, oral, intravenous, intraperitoneal, or intramuscular.

20 By "effective amount" is meant the amount of rifalazil required to treat or prevent an infection or a disease associated with an infection. The effective amount of rifalazil used to practice the present invention for therapeutic or prophylactic treatment of conditions caused by or contributed to by a microbial infection varies depending upon the manner of administration, the age, body  
25 weight, and general health of the subject. Ultimately, the attending physician will decide the appropriate amount and dosage regimen. Such amount is referred to as an "effective" amount.

By "aqueous solution" is meant an aqueous liquid that is greater than 40% water by volume and without undissolved solids above 0.5 microns in size.

Desirably, in aqueous solutions of rifalazil the rifalazil is completely dissolved.

Optionally, the rifalazil is dissolved in a micellar phase in the solution.

- 5 By "micellar phase" is meant the hydrophobic interior of an aggregate (micelle) comprising surfactant molecules.

- By "suitable for intravenous administration to a human" is meant an aqueous solution including rifalazil and one or more pharmaceutically acceptable excipients. Solutions that are suitable for intravenous administration to a human  
10 do not include excipients that would compromise the health of a patient. For example, certain organic solvents (e.g., dimethyl sulfoxide, ethanol, propanol, acetone, and dimethyl formamide) are miscible in water and useful for the preparation of aqueous solutions of insoluble compounds. However, these organic solvents are poisons in the amounts required for the formulation of rifalazil and,  
15 therefore, could not be administered intravenously to a patient without compromising the health of the patient.

By "bolus" injection or administration is meant an intravenous administration of rifalazil wherein a dose of greater than 2 mg of rifalazil is administered over a period of less than one hour.

- 20 By "infusion" is meant a continuous intravenous administration of rifalazil over a period of greater than one hour wherein rifalazil is administered at a constant rate.

### **Brief Description of the Drawings**

- 25 FIGURE 1 is a graph of the solubility of rifalazil in water as a function of pH.

FIGURE 2 is a graph depicting the solubility of rifalazil in Solvent-Water mixtures.



FIGURE 3 is a graph depicting the influence of solubilizing agents on the solubility of rifalazil in water.

FIGURE 4 is a graph depicting the solubility of rifalazil in aqueous solutions containing lipophilic salts. DTAB = Dodecyltrimethylammonium bromide; Cheno = Sodium Chenodeoxycholate; Octyl = Sodium Octylsulfate; Deoxy = Sodium Deoxycholate; Cholate = Sodium Cholate; SDS = Sodium Dodecylsulfate.

FIGURE 5 is a graph depicting the solubility of rifalazil in aqueous solutions containing varying amounts of sodium docecylsulfate at pH 5.4 and 7.4.

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### Detailed Description

The present invention provides intravenous dosage formulations of rifalazil that are suitable for administration to a human.

### 15 Formulation

Rifalazil is virtually insoluble in water at physiological pH, and the minimum desired concentration of rifalazil for intravenous administration is 100 µg/mL. This concentration is 5,000 times greater than the solubility of the drug in pH 7 buffer and 10,000 times greater than its solubility in water (see FIG. 1). In order to provide a reasonable safety margin for an intravenous dosage form of rifalazil, the target solubility at room temperature, allowing for solubility changes due to extremes of temperature, is set at a value five to ten times higher, or 0.5 to 1.0 mg/mL.

Solubilizing excipients can be used for the preparation of an intravenous dosage formulation of rifalazil. The excipients used are restricted to those that have a high degree of safety in humans.

Solubilization is taken to mean an improvement in the solubility by virtue of surface-active compounds that can convert substances that are insoluble or

virtually insoluble in water into clear, or opalescent, aqueous solutions without changing the chemical structure of these substances in the process.

The solubilizates formed are notable for the fact that the substance is present in dissolved form in the molecular associations, micelles, of the surface-active compounds, which form in aqueous solution (see FIGS. 2-5). The resulting solutions appear optically clear to opalescent.

A variety of solubilizers may be used for the formulation of rifalazil including those solubilizers disclosed in U.S. Patent No. 6,365,637, herein incorporated by reference, proteins which readily bind lipophilic compound such as albumin, and compounds belonging to the following classes: polyethoxylated fatty acids, PEG-fatty acid diesters, PEG-fatty acid mono-ester and di-ester mixtures, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglycerized fatty acids, propylene glycol fatty acid esters, mixtures of propylene glycol esters and glycerol esters, mono- and diglycerides, sterol and sterol derivatives, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, sugar esters, polyethylene glycol alkyl phenols, polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters, lower alcohol fatty acid esters, and ionic surfactants. Commercially available examples for each class of excipient are provided below.

Polyethoxylated fatty acids may be used as excipients for the formulation of rifalazil. Examples of commercially available polyethoxylated fatty acid monoester surfactants include: PEG 4-100 monolaurate (Crodet L series, Croda), PEG 4-100 monooleate (Crodet O series, Croda), PEG 4-100 monostearate (Crodet S series, Croda, and Myrj Series, Atlas/ICI), PEG 400 distearate (Cithrol 4DS series, Croda), PEG 100, 200, or 300 monolaurate (Cithrol ML series, Croda), PEG 100, 200, or 300 monooleate (Cithrol MO series, Croda), PEG 400 dioleate (Cithrol 4DO series, Croda), PEG 400-1000 monostearate (Cithrol MS series, Croda), PEG-1 stearate (Nikkol MYS-1EX, Nikko, and Coster K1,

Condea), PEG-2 stearate (Nikkol MYS-2, Nikko), PEG-2 oleate (Nikkol MYO-2, Nikko), PEG-4 laurate (Mapeg® 200 ML, PPG), PEG-4 oleate (Mapeg® 200 MO, PPG), PEG-4 stearate (Kessco® PEG 200 MS, Stepan), PEG-5 stearate (Nikkol TMGS-5, Nikko), PEG-5 oleate (Nikkol TMGO-5, Nikko), PEG-6 oleate (Algon  
5 OL 60, Auschem SpA), PEG-7 oleate (Algon OL 70, Auschem SpA), PEG-6 laurate (Kessco® PEG300 ML, Stepan), PEG-7 laurate (Lauridac 7, Condea), PEG-6 stearate (Kessco® PEG300 MS, Stepan), PEG-8 laurate (Mapeg® 400 ML, PPG), PEG-8 oleate (Mapeg® 400 MO, PPG), PEG-8 stearate (Mapeg® 400 MS, PPG), PEG-9 oleate (Emulgante A9, Condea), PEG-9 stearate (Cremophor  
10 S9, BASF), PEG-10 laurate (Nikkol MYL-10, Nikko), PEG-10 oleate (Nikkol MYO-10, Nikko), PEG-12 stearate (Nikkol MYS-10, Nikko), PEG-12 laurate (Kessco® PEG 600 ML, Stepan), PEG-12 oleate (Kessco® PEG 600 MO, Stepan), PEG-12 ricinoleate (CAS # 9004-97-1), PEG-12 stearate (Mapeg® 600 MS, PPG), PEG-15 stearate (Nikkol TMGS-15, Nikko), PEG-15 oleate (Nikkol  
15 TMGO-15, Nikko), PEG-20 laurate (Kessco® PEG 1000 ML, Stepan), PEG-20 oleate (Kessco® PEG 1000 MO, Stepan), PEG-20 stearate (Mapeg® 1000 MS, PPG), PEG-25 stearate (Nikkol MYS-25, Nikko), PEG-32 laurate (Kessco® PEG 1540 ML, Stepan), PEG-32 oleate (Kessco® PEG 1540 MO, Stepan), PEG-32 stearate (Kessco® PEG 1540 MS, Stepan), PEG-30 stearate (Myrj 51), PEG-40  
20 laurate (Crodet L40, Croda), PEG-40 oleate (Crodet O40, Croda), PEG-40 stearate (Emerest® 2715, Henkel), PEG-45 stearate (Nikkol MYS-45, Nikko), PEG-50 stearate (Myrj 53), PEG-55 stearate (Nikkol MYS-55, Nikko), PEG-100 oleate (Crodet O-100, Croda), PEG-100 stearate (Ariacel 165, ICI), PEG-200 oleate (Albunol 200 MO, Taiwan Surf.), PEG-400 oleate (LACTOMUL, Henkel), and  
25 PEG-600 oleate (Albunol 600 MO, Taiwan Surf.). Formulations of rifalazil according to the invention may include one or more of the polyethoxylated fatty acids above.

Polyethylene glycol fatty acid diesters may be used as excipients for the

formulation of rifalazil. Examples of commercially available polyethylene glycol fatty acid diesters include: PEG-4 dilaurate (Mapeg® 200 DL, PPG), PEG-4 dioleate (Mapeg® 200 DO, PPG), PEG-4 distearate (Kessco® 200 DS, Stepan), PEG-6 dilaurate (Kessco® PEG 300 DL, Stepan), PEG-6 dioleate (Kessco® PEG 300 DO, Stepan), PEG-6 distearate (Kessco® PEG 300 DS, Stepan); PEG-8 dilaurate (Mapeg® 400 DL, PPG), PEG-8 dioleate (Mapeg® 400 DO, PPG), PEG-8 distearate (Mapeg® 400 DS, PPG), PEG-10 dipalmitate (Polyaldo 2PKFG), PEG-12 dilaurate (Kessco® PEG 600 DL, Stepan), PEG-12 distearate (Kessco® PEG 600 DS, Stepan), PEG-12 dioleate (Mapeg® 600 DO, PPG), PEG-20 dilaurate (Kessco® PEG 1000 DL, Stepan), PEG-20 dioleate (Kessco® PEG 1000 DO, Stepan), PEG-20 distearate (Kessco® PEG 1000 DS, Stepan), PEG-32 dilaurate (Kessco® PEG 1540 DL, Stepan), PEG-32 dioleate (Kessco® PEG 1540 DO, Stepan), PEG-32 distearate (Kessco® PEG 1540 DS, Stepan), PEG-400 dioleate (Cithrol 4DO series, Croda), and PEG-400 distearate Cithrol 4DS series, Croda). Formulations of rifalazil according to the invention may include one or more of the polyethylene glycol fatty acid diesters above.

PEG-fatty acid mono- and di-ester mixtures may be used as excipients for the formulation of rifalazil. Examples of commercially available PEG-fatty acid mono- and di-ester mixtures include: PEG 4-150 mono, dilaurate (Kessco® PEG 200-6000 mono, Dilaurate, Stepan), PEG 4-150 mono, dioleate (Kessco® PEG 200-6000 mono, Dioleate, Stepan), and PEG 4-150 mono, distearate (Kessco® 200-6000 mono, Distearate, Stepan). Formulations of rifalazil according to the invention may include one or more of the PEG-fatty acid mono- and di-ester mixtures above.

Polyethylene glycol glycerol fatty acid esters may be used as excipients for the formulation of rifalazil. Examples of commercially available polyethylene glycol glycerol fatty acid esters include: PEG-20 glyceryl laurate (Tagat® L, Goldschmidt), PEG-30 glyceryl laurate (Tagat® L2, Goldschmidt), PEG-15

glyceryl laurate (Glycerox L series, Croda), PEG-40 glyceryl laurate (Glycerox L series, Croda), PEG-20 glyceryl stearate (Capmul® EMG, ABITEC), and Aldo® MS-20 KFG, Lonza), PEG-20 glyceryl oleate (Tagat® O, Goldschmidt), and PEG-30 glyceryl oleate (Tagat® O2, Goldschmidt). Formulations of rifalazil  
5 according to the invention may include one or more of the polyethylene glycol glycerol fatty acid esters above.

Alcohol-oil transesterification products may be used as excipients for the formulation of rifalazil. Examples of commercially available alcohol-oil transesterification products include: PEG-3 castor oil (Nikkol CO-3, Nikko), PEG-  
10 5, 9, and 16 castor oil (ACCONON CA series, ABITEC), PEG-20 castor oil, (Emalex C-20, Nihon Emulsion), PEG-23 castor oil (Emulgante EL23), PEG-30 castor oil (Incrocas 30, Croda), PEG-35 castor oil (Incrocas-35, Croda), PEG-38 castor oil (Emulgante EL 65, Condea), PEG-40 castor oil (Emalex C-40, Nihon Emulsion), PEG-50 castor oil (Emalex C-50, Nihon Emulsion), PEG-56 castor oil  
15 (Eumulgin® PRT 56, Pulcra SA), PEG-60 castor oil (Nikkol CO-60TX, Nikko), PEG-100 castor oil, PEG-200 castor oil (Eumulgin® PRT 200, Pulcra SA), PEG-5 hydrogenated castor oil (Nikkol HCO-5, Nikko), PEG-7 hydrogenated castor oil (Cremophor WO7, BASF), PEG-10 hydrogenated castor oil (Nikkol HCO-10, Nikko), PEG-20 hydrogenated castor oil (Nikkol HCO-20, Nikko), PEG-25  
20 hydrogenated castor oil (Simulsol® 1292, Seppic), PEG-30 hydrogenated castor oil (Nikkol HCO-30, Nikko), PEG-40 hydrogenated castor oil (Cremophor RH 40, BASF), PEG-45 hydrogenated castor oil (Cerex ELS 450, Auschem Spa), PEG-50 hydrogenated castor oil (Emalex HC-50, Nihon Emulsion), PEG-60 hydrogenated castor oil (Nikkol HCO-60, Nikko), PEG-80 hydrogenated castor oil (Nikkol  
25 HCO-80, Nikko), PEG-100 hydrogenated castor oil (Nikkol HCO-100, Nikko), PEG-6 corn oil (Labrafil® M 2125 CS, Gattefosse), PEG-6 almond oil (Labrafil® M 1966 CS, Gattefosse), PEG-6 apricot kernel oil (Labrafil® M 1944 CS, Gattefosse), PEG-6 olive oil (Labrafil® M 1980 CS, Gattefosse), PEG-6 peanut oil

(Labrafil® M 1969 CS, Gattefosse), PEG-6 hydrogenated palm kernel oil (Labrafil® M 2130 BS, Gattefosse), PEG-6 palm kernel oil (Labrafil® M 2130 CS, Gattefosse), PEG-6 triolein (Labrafil® M 2735 CS, Gattefosse), PEG-8 corn oil (Labrafil® WL 2609 BS, Gattefosse), PEG-20 corn glycerides (Crovol M40, 5 Croda), PEG-20 almond glycerides (Crovol A40, Croda), PEG-25 trioleate (TAGAT® TO, Goldschmidt), PEG-40 palm kernel oil (Crovol PK-70), PEG-60 corn glycerides (Crovol M70, Croda), PEG-60 almond glycerides (Crovol A70, Croda), PEG-4 caprylic/capric triglyceride (Labrafac® Hydro, Gattefosse), PEG-8 caprylic/capric glycerides (Labrasol, Gattefosse), PEG-6 caprylic/capric glycerides 10 (SOFTIGEN®767, Huls), lauroyl macrogol-32 glyceride (GELUCIRE 44/14, Gattefosse), stearyl macrogol glyceride (GELUCIRE 50/13, Gattefosse), mono, di, tri, tetra esters of vegetable oils and sorbitol (SorbitoGlyceride, Gattefosse), pentaerythrityl tetraisostearate (Crodamol PTIS, Croda), pentaerythrityl distearate (Albunol DS, Taiwan Surf.), pentaerythrityl tetraoleate (Liponate PO-4, Lipo 15 Chem.), pentaerythrityl tetrastearate (Liponate PS-4, Lipo Chem.), pentaerythrityl tetracaprylate tetracaprate (Liponate PE-810, Lipo Chem.), and pentaerythrityl tetraoctanoate (Nikkol Pentarate 408, Nikko). Also included as oils in this category of surfactants are oil-soluble vitamins, such as vitamins A, D, E, K, etc. Thus, derivatives of these vitamins, such as tocopheryl PEG-1000 succinate 20 (TPGS, available from Eastman), are also suitable surfactants. Formulations of rifalazil according to the invention may include one or more of the alcohol-oil transesterification products above.

Polyglycerized fatty acids may be used as excipients for the formulation of rifalazil. Examples of commercially available polyglycerized fatty acids include: 25 polyglyceryl-2 stearate (Nikkol DGMS, Nikko), polyglyceryl-2 oleate (Nikkol DGMO, Nikko), polyglyceryl-2 isostearate (Nikkol DGMIS, Nikko), polyglyceryl-3 oleate (Caprol® 3GO, ABITEC), polyglyceryl-4 oleate (Nikkol Tetraglyn 1-O, Nikko), polyglyceryl-4 stearate (Nikkol Tetraglyn 1-S, Nikko),

polyglyceryl-6 oleate (Drempol 6-1-O, Stepan), polyglyceryl-10 laurate (Nikkol Decaglyn 1-L, Nikko), polyglyceryl-10 oleate (Nikkol Decaglyn 1-O, Nikko), polyglyceryl-10 stearate (Nikkol Decaglyn 1-S, Nikko), polyglyceryl-6 ricinoleate (Nikkol Hexaglyn PR-15, Nikko), polyglyceryl-10 linoleate (Nikkol Decaglyn 1-5 LN, Nikko), polyglyceryl-6 pentaoleate (Nikkol Hexaglyn 5-O, Nikko), polyglyceryl-3 dioleate (Cremophor GO32, BASF), polyglyceryl-3 distearate (Cremophor GS32, BASF), polyglyceryl-4 pentaoleate (Nikkol Tetraglyn 5-O, Nikko), polyglyceryl-6 dioleate (Caprol® 6G20, ABITEC), polyglyceryl-2 dioleate (Nikkol DGDO, Nikko), polyglyceryl-10 trioleate (Nikkol Decaglyn 3-O, 10 Nikko), polyglyceryl-10 pentaoleate (Nikkol Decaglyn 5-O, Nikko), polyglyceryl-10 septaoleate (Nikkol Decaglyn 7-O, Nikko), polyglyceryl-10 tetraoleate (Caprol® 10G4O, ABITEC), polyglyceryl-10 decaisostearate (Nikkol Decaglyn 10-IS, Nikko), polyglyceryl-101 decaoleate (Drempol 10-10-O, Stepan), polyglyceryl-10 mono, dioleate (Caprol® PGE 860, ABITEC), and polyglyceryl 15 polyricinoleate (Polymuls, Henkel). Formulations of rifalazil according to the invention may include one or more of the polyglycerized fatty acids above.

Propylene glycol fatty acid esters may be used as excipients for the formulation of rifalazil. Examples of commercially available propylene glycol fatty acid esters include: propylene glycol monocaprylate (Capryol 90, 20 Gattefosse), propylene glycol monolaurate (Lauroglycol 90, Gattefosse), propylene glycol oleate (Lutrol OP2000, BASF), propylene glycol myristate (Mirpyl), propylene glycol monostearate (LIPO PGMS, Lipo Chem.), propylene glycol hydroxystearate, propylene glycol ricinoleate (PROPYMULS, Henkel), propylene glycol isostearate, propylene glycol monooleate (Myverol P-O6, 25 Eastman), propylene glycol dicaprylate dicaprate (Captex® 200, ABITEC), propylene glycol dioctanoate (Captex® 800, ABITEC), propylene glycol caprylate caprate (LABRAFAC PG, Gattefosse), propylene glycol dilaurate, propylene glycol distearate (Kessco® PGDS, Stepan), propylene glycol dicaprylate (Nikkol

Sefsol 228, Nikko), and propylene glycol dicaprate (Nikkol PDD, Nikko).

Formulations of rifalazil according to the invention may include one or more of the propylene glycol fatty acid esters above.

Mixtures of propylene glycol esters and glycerol esters may be used as  
5 excipients for the formulation of rifalazil. One preferred mixture is composed of the oleic acid esters of propylene glycol and glycerol (Arlacel 186). Examples of these surfactants include: oleic (ATMOS 300, ARLACEL 186, ICI), stearic (ATMOS 150). Formulations of rifalazil according to the invention may include one or more of the mixtures of propylene glycol esters and glycerol esters above.

10 Mono- and diglycerides may be used as excipients for the formulation of rifalazil. Examples of commercially available mono- and diglycerides include: monopalmitolein (C16:1) (Larodan), monoelaidin (C18:1) (Larodan), monocaproin (C6) (Larodan), monocaprylin (Larodan), monocaprin (Larodan), monolaurin (Larodan), glyceryl monomyristate (C14) (Nikkol MGM, Nikko),  
15 glyceryl monooleate (C18:1) (PECEOL, Gattefosse), glyceryl monooleate (Myverol, Eastman), glycerol monooleate/linoleate (OLICINE, Gattefosse), glycerol monolinoleate (Maisine, Gattefosse), glyceryl ricinoleate (Softigen® 701, Huls), glyceryl monolaurate (ALDO® MLD, Lonza), glycerol monopalmitate (Emalex GMS-P, Nihon), glycerol monostearate (Capmul® GMS, ABITEC),  
20 glyceryl mono- and dioleate (Capmul® GMO-K, ABITEC), glyceryl palmitic/stearic (CUTINA MD-A, ESTAGEL-G18), glyceryl acetate (Lamegin® EE, Grunau GmbH), glyceryl laurate (Imwitor® 312, Huls), glyceryl citrate/lactate/oleate/linoleate (Imwitor® 375, Huls), glyceryl caprylate (Imwitor® 308, Huls), glyceryl caprylate/caprinate (Capmul® MCM, ABITEC), caprylic acid  
25 mono- and diglycerides (Imwitor® 988, Huls), caprylic/capric glycerides (Imwitor® 742, Huls), Mono- and diacetylated monoglycerides (Myvacet® 9-45, Eastman), glyceryl monostearate (Aldo® MS, Arlacel 129, ICI), lactic acid esters of mono and diglycerides (LAMEGIN GLP, Henkel), dicaproin (C6) (Larodan),



dicaprin (C10) (Larodan), dioctanoin (C8) (Larodan), dimyristin (C14) (Larodan), dipalmitin (C16) (Larodan), distearin (Larodan), glyceryl dilaurate (C12) (Capmul® GDL, ABITEC), glyceryl dioleate (Capmul® GDO, ABITEC), glycerol esters of fatty acids (GELUCIRE 39/01, Gattefosse), dipalmitolein 5 (C16:1) (Larodan), 1,2 and 1,3-diolein (C18:1) (Larodan), dielaidin (C18:1) (Larodan), and dilinolein (C18:2) (Larodan). Formulations of rifalazil according to the invention may include one or more of the mono- and diglycerides above.

Sterol and sterol derivatives may be used as excipients for the formulation of rifalazil. Examples of commercially available sterol and sterol derivatives 10 include: cholesterol, sitosterol, lanosterol, PEG-24 cholesterol ether (Solulan C-24, Amerchol), PEG-30 cholestanol (Phytosterol GENEROL series, Henkel), PEG-25 phytosterol (Nikkol BPSH-25, Nikko), PEG-5 soyasterol (Nikkol BPS-5, Nikko), PEG-10 soyasterol (Nikkol BPS-10, Nikko), PEG-20 soyasterol (Nikkol BPS-20, Nikko), and PEG-30 soyasterol (Nikkol BPS-30, Nikko). Formulations of rifalazil 15 according to the invention may include one or more of the sterol and sterol derivatives above.

Polyethylene glycol sorbitan fatty acid esters may be used as excipients for the formulation of rifalazil. Examples of commercially available polyethylene glycol sorbitan fatty acid esters include: PEG-10 sorbitan laurate (Liposorb L-10, 20 Lipo Chem.), PEG-20 sorbitan monolaurate (Tween® 20, Atlas/ICI), PEG-4 sorbitan monolaurate (Tween® 21, Atlas/ICI), PEG-80 sorbitan monolaurate (Hodag PSML-80, Calgene), PEG-6 sorbitan monolaurate (Nikkol GL-1, Nikko), PEG-20 sorbitan monopalmitate (Tween® 40, Atlas/ICI), PEG-20 sorbitan monostearate (Tween® 60, Atlas/ICI), PEG-4 sorbitan monostearate (Tween® 61, 25 Atlas/ICI), PEG-8 sorbitan monostearate (DACOL MSS, Condea), PEG-6 sorbitan monostearate (Nikkol TS106, Nikko), PEG-20 sorbitan tristearate (Tween® 65, Atlas/ICI), PEG-6 sorbitan tetrastearate (Nikkol GS-6, Nikko), PEG-60 sorbitan tetrastearate (Nikkol GS-460, Nikko), PEG-5 sorbitan monooleate (Tween® 81,

Atlas/ICI), PEG-6 sorbitan monooleate (Nikkol TO-106, Nikko), PEG-20 sorbitan monooleate (Tween® 80, Atlas/ICI), PEG-40 sorbitan oleate (Emalex ET 8040, Nihon Emulsion), PEG-20 sorbitan trioleate (Tween® 85, Atlas/ICI), PEG-6 sorbitan tetraoleate (Nikkol GO-4, Nikko), PEG-30 sorbitan tetraoleate (Nikkol GO-430, Nikko), PEG-40 sorbitan tetraoleate (Nikkol GO-440, Nikko), PEG-20 sorbitan monoisostearate (Tween® 120, Atlas/ICI), PEG sorbitol hexaoleate (Atlas G-1086, ICI), polysorbate 80 (Tween® 80, Pharma), polysorbate 85 (Tween® 85, Pharma), polysorbate 20 (Tween® 20, Pharma), polysorbate 40 (Tween® 40, Pharma), polysorbate 60 (Tween® 60, Pharma), and PEG-6 sorbitol hexastearate (Nikkol GS-6, Nikko). Formulations of rifalazil according to the invention may include one or more of the polyethylene glycol sorbitan fatty acid esters above.

Polyethylene glycol alkyl ethers may be used as excipients for the formulation of rifalazil. Examples of commercially available polyethylene glycol alkyl ethers include: PEG-2 oleyl ether, oleth-2 (Brij 92/93, Atlas/ICI), PEG-3 oleyl ether, oleth-3 (Volpo 3, Croda), PEG-5 oleyl ether, oleth-5 (Volpo 5, Croda), PEG-10 oleyl ether, oleth-10 (Volpo 10, Croda), PEG-20 oleyl ether, oleth-20 (Volpo 20, Croda), PEG-4 lauryl ether, laureth-4 (Brij 30, Atlas/ICI), PEG-9 lauryl ether, PEG-23 lauryl ether, laureth-23 (Brij 35, Atlas/ICI), PEG-2 cetyl ether (Brij 52, ICI), PEG-10 cetyl ether (Brij 56, ICI), PEG-20 cetyl ether (Brij 58, ICI), PEG-2 stearyl ether (Brij 72, ICI), PEG-10 stearyl ether (Brij 76, ICI), PEG-20 stearyl ether (Brij 78, ICI), and PEG-100 stearyl ether (Brij 700, ICI). Formulations of rifalazil according to the invention may include one or more of the polyethylene glycol alkyl ethers above.

Sugar esters may be used as excipients for the formulation of rifalazil. Examples of commercially available sugar esters include: sucrose distearate (SUCRO ESTER 7, Gattefosse), sucrose distearate/monostearate (SUCRO ESTER 11, Gattefosse), sucrose dipalmitate, sucrose monostearate (Crodesta F-160,

Croda), sucrose monopalmitate (SUCRO ESTER 15, Gattefosse), and sucrose monolaurate (Saccharose monolaurate 1695, Mitsubisbi-Kasei). Formulations of rifalazil according to the invention may include one or more of the sugar esters above.

5 Polyethylene glycol alkyl phenols may be used as excipients for the formulation of rifalazil. Examples of commercially available polyethylene glycol alkyl phenols include: PEG-10-100 nonylphenol series (Triton X series, Rohm & Haas) and PEG-15-100 octylphenol ether series (Triton N-series, Rohm & Haas). Formulations of rifalazil according to the invention may include one or more of  
10 the polyethylene glycol alkyl phenols above.

Polyoxyethylene-polyoxypropylene block copolymers may be used as excipients for the formulation of rifalazil. These surfactants are available under various trade names, including one or more of Synperonic PE series (ICI), Pluronic® series (BASF), Lutrol (BASF), Supronic, Monolan, Pluracare, and  
15 Plurodac. The generic term for these polymers is "poloxamer" (CAS 9003-11-6). These polymers have the formula I:



I

20 where "a" and "b" denote the number of polyoxyethylene and polyoxypropylene units, respectively. Formulations of rifalazil according to the invention may include one or more of the polyoxyethylene-polyoxypropylene block copolymers above.

Polyoxyethylenes, such as PEG 300, PEG 400, and PEG 600, may be used  
25 as excipients for the formulation of rifalazil.

Sorbitan fatty acid esters may be used as excipients for the formulation of rifalazil. Examples of commercially sorbitan fatty acid esters include: sorbitan monolaurate (Span-20, Atlas/ICI), sorbitan monopalmitate (Span-40, Atlas/ICI),

sorbitan monooleate (Span-80, Atlas/ICI), sorbitan monostearate (Span-60, Atlas/ICI), sorbitan trioleate (Span-85, Atlas/ICI), sorbitan sesquioleate (Arlacel-C, ICI), sorbitan tristearate (Span-65, Atlas/ICI), sorbitan monoisostearate (Crill 6, Croda), and sorbitan sesquistearate (Nikkol SS-15, Nikko). Formulations of  
5 rifalazil according to the invention may include one or more of the sorbitan fatty acid esters above.

Esters of lower alcohols (C2 to C4) and fatty acids (C8 to C18) are suitable surfactants for use in the present invention. Examples of these surfactants include: ethyl oleate (Crodamol EO, Croda), isopropyl myristate (Crodamol IPM, Croda),  
10 isopropyl palmitate (Crodamol IPP, Croda), ethyl linoleate (Nikkol VF-E, Nikko), and isopropyl linoleate (Nikkol VF-IP, Nikko). Formulations of rifalazil according to the invention may include one or more of the lower alcohol fatty acid esters above.

Ionic surfactants may be used as excipients for the formulation of rifalazil.  
15 Examples of useful ionic surfactants include: sodium caproate, sodium caprylate, sodium caprate, sodium laurate, sodium myristate, sodium myristolate, sodium palmitate, sodium palmitoleate, sodium oleate, sodium ricinoleate, sodium linoleate, sodium linolenate, sodium stearate, sodium lauryl sulfate (dodecyl), sodium tetradecyl sulfate, sodium lauryl sarcosinate, sodium dioctyl  
20 sulfosuccinate, sodium cholate, sodium taurocholate, sodium glycocholate, sodium deoxycholate, sodium taurodeoxycholate, sodium glycodeoxycholate, sodium ursodeoxycholate, sodium chenodeoxycholate, sodium taurochenodeoxycholate, sodium glyco cheno deoxycholate, sodium cholylsarcosinate, sodium N-methyl taurocholate, egg yolk phosphatides, hydrogenated soy lecithin, dimyristoyl  
25 lecithin, lecithin, hydroxylated lecithin, lysophosphatidylcholine, cardiolipin, sphingomyelin, phosphatidylcholine, phosphatidyl ethanolamine, phosphatidic acid, phosphatidyl glycerol, phosphatidyl serine, diethanolamine, phospholipids, polyoxyethylene-10 oleyl ether phosphate, esterification products of fatty alcohols

or fatty alcohol ethoxylates, with phosphoric acid or anhydride, ether carboxylates (by oxidation of terminal OH group of, fatty alcohol ethoxylates), succinylated monoglycerides, sodium stearyl fumarate, stearyl propylene glycol hydrogen succinate, mono/diacetylated tartaric acid esters of mono- and diglycerides, citric  
5 acid esters of mono-, diglycerides, glyceryl-lacto esters of fatty acids, acyl lactylates, lactic esters of fatty acids, sodium stearyl-2-lactylate, sodium stearyl lactylate, alginate salts, propylene glycol alginate, ethoxylated alkyl sulfates, alkyl benzene sulfones,  $\alpha$ -olefin sulfonates, acyl isethionates, acyl taurates, alkyl glyceryl ether sulfonates, sodium octyl sulfosuccinate, sodium  
10 undecylenamideo-MEA-sulfosuccinate, hexadecyl triammonium bromide, decyl trimethyl ammonium bromide, cetyl trimethyl ammonium bromide, dodecyl ammonium chloride, alkyl benzyldimethylammonium salts, diisobutyl phenoxyethoxydimethyl benzylammonium salts, alkylpyridinium salts, betaines (trialkylglycine), lauryl betaine (N-lauryl,N,N-dimethylglycine), and ethoxylated  
15 amines (polyoxyethylene-15 coconut amine). For simplicity, typical counterions are provided above. It will be appreciated by one skilled in the art, however, that any bioacceptable counterion may be used. For example, although the fatty acids are shown as sodium salts, other cation counterions can also be used, such as, for example, alkali metal cations or ammonium. Formulations of rifalazil according  
20 to the invention may include one or more of the ionic surfactants above.

The surfactants present in the formulations of the present invention are present in amounts such that the carrier forms a clear, or opalescent, aqueous dispersion of rifalazil. The relative amounts of surfactants required are readily determined by observing the solubility properties of the resultant rifalazil  
25 dispersion, as determined using standard techniques for measuring solubilities. The optical clarity of the aqueous dispersion can be measured using standard quantitative techniques for turbidity assessment.

Methods for making formulations are found, for example, in "Remington: The Science and Practice of Pharmacy" (20th ed., ed. A.R. Gennaro AR., 2000, Lippincott Williams & Wilkins). Formulations for parenteral administration may, for example, contain any of the excipients described above, sterile water, isotonic  
5 saline, isotonic dextrose solution, or nutritional supplements such as glucose. Alternatively, nanoparticulate formulations (e.g., biodegradable nanoparticles, solid lipid nanoparticles) may be used to prepare an intravenous dosage form of rifalazil. Other potentially useful parenteral delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems,  
10 and liposomes.

### Combination Therapy

Rifalazil can be formulated in combination or administered in parallel with other drugs such as amikacin, gentamicin, kanamycin, azithromycin, tetracycline,  
15 vancomycin, or teicoplanin, with other rifamycin-class antibiotics, with other antibacterial agents, or, for example, with analgesics or antitussives.

Antibiotics that can be administered in combination or in parallel with rifalazil include: aminoglycosides, such as amikacin, apramycin, arbekacin, bambermycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin(s),  
20 fradiomycin, gentamicin, isipamicin, kanamycin, micronomicin, neomycin, neomycin undecylenate, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, streptonicozid, and tobramycin; amphenicols, such as azidamfenicol, chloramphenicol, chloramphenicol palmirate, chloramphenicol pantothenate, florfenicol, and thiamphenicol; ansamycins, such as rifampin,  
25 rifabutin, rifapentine, and rifaximin;  $\beta$ -Lactams, such as amidinocillin, amdinocillin, pivoxil, amoxicillin, ampicillin, aspoxicillin, azidocillin, azlocillin, bacampicillin, benzylpenicillinic acid, benzylpenicillin, carbenicillin, carfecillin, carindacillin, clometocillin, cloxacillin, cyclacillin, dicloxacillin, diphenicillin,

epicillin, fenbenicillin, floxicillin, hetacillin, lenampicillin, metampicillin,  
 methicillin, mezlocillin, nafcillin, oxacillin, penamecillin, penethamate hydriodide,  
 penicillin G benethamine, penicillin G benzathine, penicillin G benzhydrylamine,  
 penicillin G calcium, penicillin G hydragamine, penicillin G potassium, penicillin  
 5 G, procaine, penicillin N, penicillin O, penicillin V, penicillin V benzathine,  
 penicillin V hydrabamine, penimepicycline, phenethicillin, piperacillin,  
 pivapicillin, propicillin, quinacillin, sulbenicillin, talampicillin, temocillin and  
 ticarcillin; carbapenems, such as imipenem; cephalosporins, such as 1-Carba  
 (dethia) cephalosporin, cefactor, cefadroxil, cefamandole, cefatrizine, cefazedone,  
 10 cefazolin, cefixime, Cefmenoxime, Cefodizime, Cefonicid, cefoperazone,  
 ceforanide, cefotaxime, cefotiam, cefpimizole, cefpirimide, cefpodoxime proxetil,  
 cefroxadine, cefsulodin, ceftazidime, cefteteram, ceftazole, ceftibuten, ceftizoxime,  
 ceftriaxone, cefuroxime, cefuzonam, cephradine sodium, cephalixin,  
 cephaloglycin, cephaloridine, cephalosporin, cephalothin, cephalirin Sodium,  
 15 cephradine, pivcefalexin, cephalothin, cefaclor, cefotetan, cefprozil, loracarbef,  
 cefetamet, and cefepime; cephamycins such as cefbuperazone, cefmetazole,  
 cefminox, cefetan, and cefoxitin; monobactams such as aztreonam, carumonam,  
 and tigemonan; oxacephems such as flomoxef and moxolactam; lincosamides such  
 as clindamycin and lincomycin; macrolides such as azithromycin, carbomycin,  
 20 clarithromycin, erythromycin(s) and derivatives, josamycin, leucomycins,  
 midecamycins, miokamycin, oleandomycin, primycin, rokitamycin, rosaramicin,  
 roxithromycin, spiramycin and troleandomycin; polypeptides such as  
 amphomycin, bacitracin, capreomycin, colistin, enduracidin, enylomycin,  
 fusafungine, gramicidin(s), gramicidin S, mikamycin, polymyxin, polymyxin  $\beta$ -  
 25 methanesulfonic acid, pristnamycin, ristocetin, teicoplanin, thiostrepton,  
 tuberactinomycin, tyrocidine, tyrothricin, vancomycin, viomycin(s), virginiamycin  
 and zinc bacitracin; tetracyclines such as spicycline, chlortetracycline,  
 clomocycline, demeclocycline, doxycycline, guamecycline, lymecycline,

meclocycline, methacycline, minocycline, oxytetracycline, penimepicycline, pipacycline, rolitetracycline, sancycline, senociclin and tetracycline; and 2,4-Diaminopyrimidines such as brodimoprim, tetroxoprim and trimethoprim; nitrofurans such as furaltadone, furazolium, nifuradene, nifuratel, nifurfoline, 5 nifurpirinol, nifurprazine, nifurtoinol and nitrofurantoin; quinolones such as amifloxacin, cinoxacin, ciprofloxacin, difloxacin, enoxacin, fleroxacin, flumequine, lomefloxacin, miloxacin, nalidixic acid, norfloxacin, ofloxacin, oxolinic acid, perfloxacin, pipemidic acid, piromidic acid, rosoxacin, temafloxacin, and tosufloxacin; sulfonamides such as acetyl

10 sulfamethoxypyrazine, acetyl sulfisoxazole, azosulfamide, benzylsulfamide, chloramine-β, chloramine-T, dichloramine-T; formosulfathiazole, N<sub>2</sub>-formyl-sulfisomidine, N<sub>4</sub>-β-D-glucosylsulfanilamide, mafenide, 4'-(methyl-sulfamoyl)sulfanilanilide, p-nitrosulfathiazole, noprilsulfamide, phthalylsulfacetamide, phthalylsulfathiazole, salazosulfadimidine,

15 succinylsulfathiazole, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanol, sulfalene, sulfaloxic acid, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfametrole, sulfamidochrysoidine,

20 sulfamoxole, sulfanilamide, sulfanilamidomethanesulfonic acid triethanolamine salt, 4-sulfanilamidosalicylic acid, N<sub>4</sub>-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfanitran, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfatolamide, sulfisomidine and sulfisoxazole; sulfones, such as

25 acedapsone, acediasulfone, acetosulfone, dapsone, diathymosulfone, glucosulfone, solasulfone, succisulfone, sulfanilic acid, p-sulfanilylbenzylamine, p,p'-sulfonyldianiline-N,N'digalactoside, sulfoxone and thiazolsulfone; lipopeptides such as daptomycin; oxazolidones such as linezolid; ketolides such as



telithromycin; and miscellaneous antibiotics such as clofoctol, hexedine, magainins, methenamine, methenamine anhydromethylene-citrate, methenamine hippurate, methenamine mandelate, methenamine sulfosalicylate, nitroxoline, squalamine, xibornol, cycloserine, mupirocin, and tuberin. Accordingly, the invention features methods of treating disease by administering rifalazil in combination or in parallel with the antibiotics above, among others.

The dosing frequency and amounts of drugs used in combination or administered in parallel will depend upon the intended use, on the patient's symptoms and severity of the disease, and are within the skills of the pharmacist, medicinal chemist, or medical practitioner formulating the rifamycin-class antibiotic in combination with other drugs.

### **Monotherapy**

Rifalazil can be used as monotherapy for the treatment and prevention of infections and infection related diseases. Rifalazil is a derivative of rifamycin that suppresses RNA synthesis, resulting in broad antimicrobial properties.

Rifalazil is distinguished from other rifamycin derivatives in that rifalazil monotherapy can be used safely and effectively for the eradication a wide range of bacterial infections without the danger of forming untreatable resistant strains. When other rifamycin derivatives (e.g., rifampin, rifabutin, rifapentine, and rifaximin) are used as monotherapy for the treatment of bacterial infections, resistance develops rapidly because of single-point mutations, resulting in the emergence of resistant strains of bacteria. Accordingly, with the exception of rifalazil, monotherapy is generally avoided for this class of antimicrobial agents.

25

### **Administration**

One of the advantages of the present invention is that the intravenous dosage formulations provide clinicians with the ability to directly adjust the

plasma levels of rifalazil to the point of therapeutic efficacy by controlling the dose and the schedule of drug administration. Adjusting the dose and schedule of drug administration as described herein can result in a superior ability to achieve a safer and more effective treatment of disease. Specifically, by avoiding high  
5 initial peak levels, peak blood level related side effects are minimized or, in some instances, eliminated.

Rifalazil can be administered by intravenous infusion, wherein between 2 and 50 mg of rifalazil is administered over a period of 4 to 24 hours. Desirably, between 4 and 40 mg, 4 and 30 mg, 6 and 30 mg, 7 and 30 mg, or 8 and 25 mg of  
10 rifalazil is administered over a period of 4 to 24 hours, 8 to 24 hours, 15 to 24 hours, or 20 to 24 hours. Up to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, or 50 mg of rifalazil is administered by intravenous infusion over a 2, 4, 5, 6, 7, 8, 9, 10, 12, 14, 20, 24, 48, or 72 hour period.

15 Alternatively, rifalazil can be administered by intravenous bolus followed by slow infusion. Desirably, a bolus injection of between 2 and 25 mg of rifalazil over a 10 to 60 minute period is followed by a slow infusion of 0.1 to 2 mg per hour for up to 24 hours.

The intravenous administration of rifalazil may be repeated daily or every  
20 other day, for a period of two to fourteen days. Desirably, the intravenous administration is repeated every third day for a period of three to fifteen days.

Adjusting the dose and schedule of drug administration as described herein, rifalazil can be intravenously administered at a rate that maintains a plasma concentration of rifalazil of between 4 and 80, 6 and 50, 10 and 50, 10 and 30  
25 ng/mL, 12 and 30 ng/mL, 6 and 25 ng/mL, 8 and 20 ng/mL, 9 and 20 ng/mL, 10 and 20 ng/mL, 11 and 20 ng/mL, or 12 and 20 ng/mL for a period greater than 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 32, 40, 48, or 72 hours.

Desirably, rifalazil is administered in a dosing schedule that maintains a plasma concentration of rifalazil of between 10 and 40 ng/mL for a period greater than 24 hours.

## 5 Packaging

The compositions of the present invention may be packaged together with instructions for the intravenous administration of a rifalazil. Typically, the instructions will also include the dosage and rate of administration. In some instances, instructions may be included on a label or on a package insert

10 accompanying an intravenous pharmaceutical formulation containing rifalazil.

The method of the present invention can be incorporated into a prepackaged therapeutic regimen designed to deliver a specific dose of rifalazil over a specific period of time to a patient. For example, a sufficient amount of rifalazil can be administered as a "push" over ten to sixty minutes to produce a desired blood level  
15 and the remainder of the dose would be administered over a period of up to a total of 24 hours at such a rate that the blood level would remain constant. In this manner rifalazil could be intravenously administered every day, every other day, or every third day for a period of up twelve days with continuing doses available orally using a weekly regimen if desired.

20

## Other Embodiments

All publications, patent applications, and patents mentioned in this specification are herein incorporated by reference.

While the invention has been described in connection with specific  
25 embodiments, it will be understood that it is capable of further modifications. Therefore, this application is intended to cover any variations, uses, or adaptations of the invention that follow, in general, the principles of the invention, including

departures from the present disclosure that come within known or customary practice within the art.

Other embodiments are within the claims. What we claim is:

## Claims

1. An aqueous solution of rifalazil suitable for intravenous administration to a human, wherein said solution has a rifalazil concentration of between 20 to 10,000  
5  $\mu\text{g/mL}$ .

2. The solution of claim 1, further comprising one or more excipients wherein the class of excipient is selected from the group consisting of polyethoxylated fatty acids, PEG-fatty acid diesters, PEG-fatty acid mono-ester and di-ester mixtures,  
10 polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglycerized fatty acids, propylene glycol fatty acid esters, mixtures of propylene glycol esters-glycerol esters, mono- and diglycerides, sterol and sterol derivatives, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, sugar esters, polyethylene glycol alkyl phenols, polyoxyethylene-  
15 polyoxypropylene block copolymers, sorbitan fatty acid esters, lower alcohol fatty acid esters, and ionic surfactants.

3. The solution of claim 1, further comprising one or more excipients selected from the group consisting of sodium lauryl sulfate, polyoxyl-40 stearate, PEG-3  
20 castor oil, PEG-5, 9, and 16 castor oil, PEG-20 castor oil, PEG-23 castor oil, PEG-30 castor oil, PEG-35 castor oil, PEG-38 castor oil, PEG-40 castor oil, PEG-50 castor oil, PEG-60 castor oil, PEG-100 castor oil, PEG-200 castor oil, PEG-5 hydrogenated castor oil, PEG-7 hydrogenated castor oil, PEG-10 hydrogenated castor oil, PEG-20 hydrogenated castor oil, PEG-25 hydrogenated castor oil, PEG-  
25 30 hydrogenated castor oil, PEG-40 hydrogenated castor oil, PEG-45 hydrogenated castor oil, PEG-50 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-80 hydrogenated castor oil, and PEG-100 hydrogenated castor oil.

4. The solution of any of claims 1-3, wherein rifalazil is contained within micelles spontaneously formed by an excipient in the solution.
5. A method of treating or preventing disease in a human, said method comprising  
5 intravenous administration of a solution comprising rifalazil to said human in amounts effective to treat or prevent said disease, wherein said solution is suitable for administration to a human.
6. The method of claims 5, wherein said disease is selected from the group  
10 consisting of respiratory tract infections, acute bacterial otitis media, bacterial pneumonia, urinary tract infections, complicated infections, noncomplicated infections, pyelonephritis, intra-abdominal infections, deep-seated abscesses, bacterial sepsis, skin and skin structure infections, soft tissue infections, bone and joint infections, central nervous system infections, bacteremia, wound infections,  
15 peritonitis, meningitis, infections after burn, urogenital tract infections, gastrointestinal tract infections, pelvic inflammatory disease, endocarditis and other intravascular infections.
7. The method of claims 5, wherein said disease is associated with bacterial  
20 infection and selected from the group consisting of atherosclerosis, multiple sclerosis, rheumatoid arthritis, diabetes, Alzheimer's disease, asthma, cirrhosis of the liver, psoriasis, meningitis, cystic fibrosis, cancer and osteoporosis.
8. The method of claim 5, wherein said rifalazil is administered for prophylaxis  
25 against infections resulting from surgical procedures and implantation of prosthetic devices.

9. The method of claim 5, wherein said disease is an infection by a bacterium belonging to a genus selected from the group consisting of *Escherichia spp.*, *Enterobacter spp.*, *Enterobacteriaceae spp.*, *Klebsiella spp.*, *Serratia spp.*, *Pseudomonas spp.*, *Acinetobacter spp.*, *Bacillus spp.*, *Micrococcus spp.*,  
5 *Arthrobacter spp.*, *Peptostreptococcus spp.*, *Staphylococcus spp.*, *Enterococcus spp.*, *Streptococcus spp.*, *Haemophilus spp.*, *Neisseria spp.*, *Bacteroides spp.*, *Citrobacter spp.*, *Branhamella spp.*, *Salmonella spp.*, *Shigella spp.*, *Proteus spp.*, *Clostridium spp.*, *Erysipelothrix spp.*, *Listeria spp.*, *Pasteurella spp.*, *Streptobacillus spp.*, *Spirillum spp.*, *Fusospirocheta spp.*, *Treponema spp.*,  
10 *Borrelia spp.*, *Actinomycetes spp.*, *Mycoplasma spp.*, *Chlamydia spp.*, *Rickettsia spp.*, *Spirochaeta spp.*, *Legionella spp.*, *Mycobacteria spp.*, *Ureaplasma spp.*, *Streptomyces spp.*, and *Trichomoras spp.*

10. A method of treating a non-mycobacterial infection by Gram-positive bacteria  
15 in a human, said method comprising administration of rifalazil to said human in amounts effective to treat said infection.

11. The method of claim 10, wherein said bacteria are selected from the group consisting of *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus*  
20 *faecalis*, *Enterococcus faecium*, *Clostridium perfringens*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, other *Streptococcus spp.*, and other *Clostridium spp.*

12. A method of treating an infection by multi-drug resistant bacteria in a human,  
said method comprising administration of rifalazil to said human in amounts  
25 effective to treat said infection.

13. The method of claim 12, wherein said multi-drug resistant bacteria are penicillin-resistant, methicillin-resistant, quinolone-resistant, macrolide-resistant, or vancomycin-resistant bacteria.
- 5 14. The method of claim 13, wherein said bacteria are selected from the group consisting of *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Enterococcus spp.*
15. The method of any of claims 10-14, wherein said administration of rifalazil  
10 comprises intravenous administration of a solution which is suitable for administration to a human.
16. The method of any one of claims 5-9 and 15, wherein said intravenous administration of rifalazil comprises intravenous infusion into said human of  
15 between 2 and 50 mg of rifalazil over a period of 4 to 24 hours.
17. The method of claim 16, wherein said intravenous administration of rifalazil comprises:
- a) a bolus injection of between 2 and 25 mg of rifalazil over 10 to 60  
20 minutes, and
- b) following step a, a slow infusion of between 0.1 and 2 mg per hour for up to 24 hours.
18. The method of claims 16 or 17, wherein said intravenous administration is  
25 repeated daily for a period of two to fourteen days.
19. The method of any of claims 5-14, wherein rifalazil is administered as a monotherapy.



20. The method of any of claims 5-14, further comprising the administration of a second antibiotic.

5 21. The method of claim 20, wherein the classs of said second antibiotic is selected from the group consisting of aminoglycosides, amphenicols, ansamycins,  $\beta$ -Lactams, carbapenems, cephalosporins, cephamycins, lincosamides, macrolides, polypeptides, tetracyclines, 2,4-Diaminopyrimidines, nitrofurans, quinolones, sulfonamides, lipopeptides, oxazolidones, ketolides and sulfones.

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22. The method of claim 21, wherein said second antibiotic is selected from the group consisting of amikacin, gentamicin, kanamycin, azithromycin, tetracycline, vancomycin, and teicoplanin.

15 23. A method of treating disease in a human, said method comprising maintaining a rifalazil concentration of between 6 and 50 ng/mL in the plasma of said human for a period greater than 5 hours.

24. A method of treating disease in a human, said method comprising maintaining  
20 a rifalazil concentration of between 10 and 30 ng/mL in the plasma of said human for a period greater than 24 hours.

25. A pharmaceutical formulation comprising rifalazil for intravenous administration, wherein said formulation is packaged with a label or package  
25 insert providing instructions for the use of said formulation, wherein the instructions describe an intravenous dosing schedule.

# **INTRAVENOUS FORMULATION OF RIFALAZIL AND METHODS OF USE THEREOF**

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## **Abstract of the Disclosure**

The invention features materials and methods for the intravenous administration of rifalazil and methods of use thereof.



FIG. 1

Solubility of Rifalazil as a Function of pH

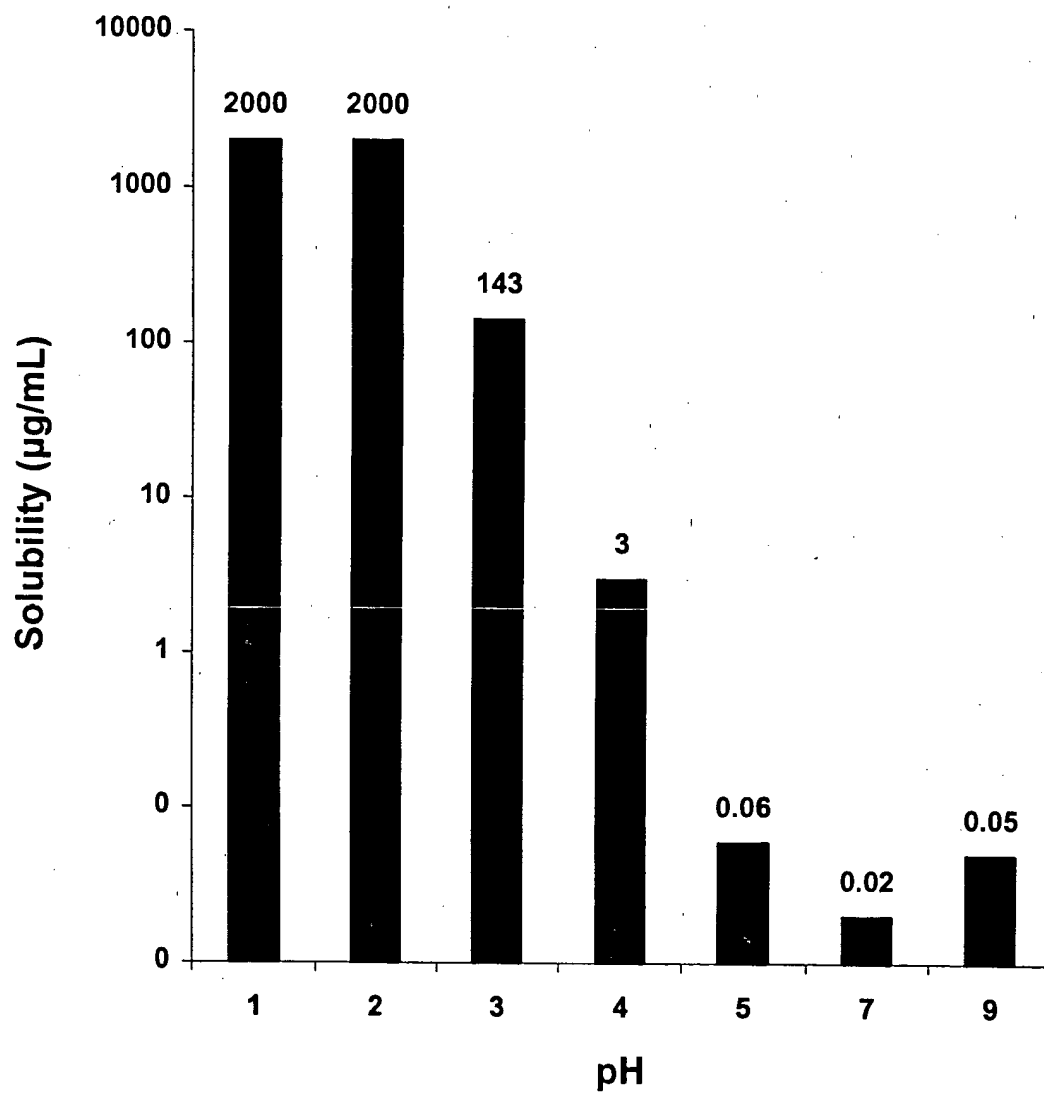


FIG. 2

Rifalazil Solubility in Solvent-Water mixtures

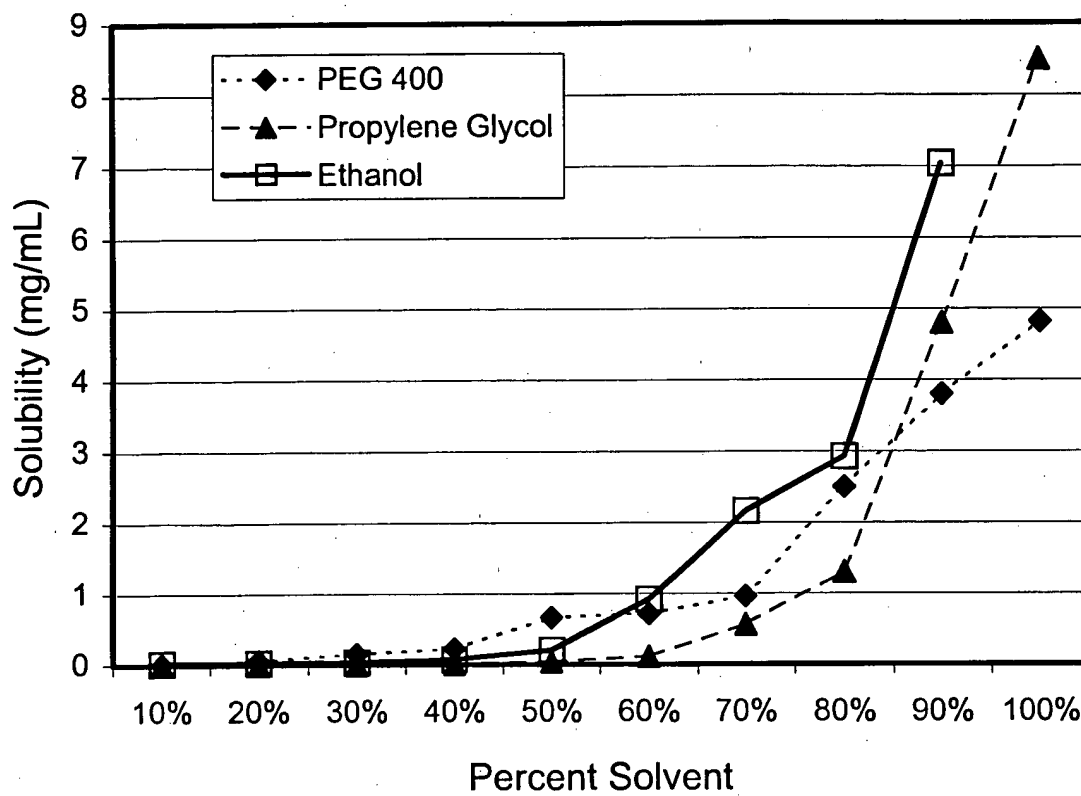


FIG. 3

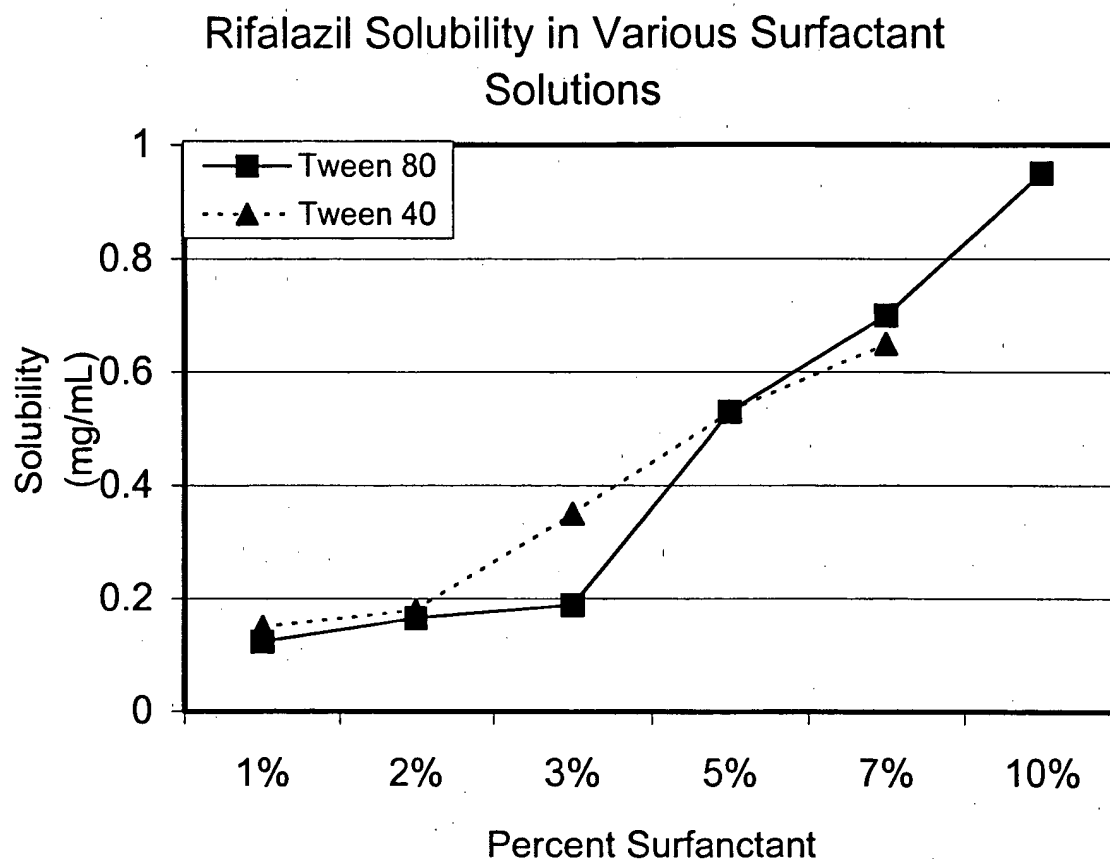


FIG. 4

### Effect of Certain Salts on Rifalazil Solubility

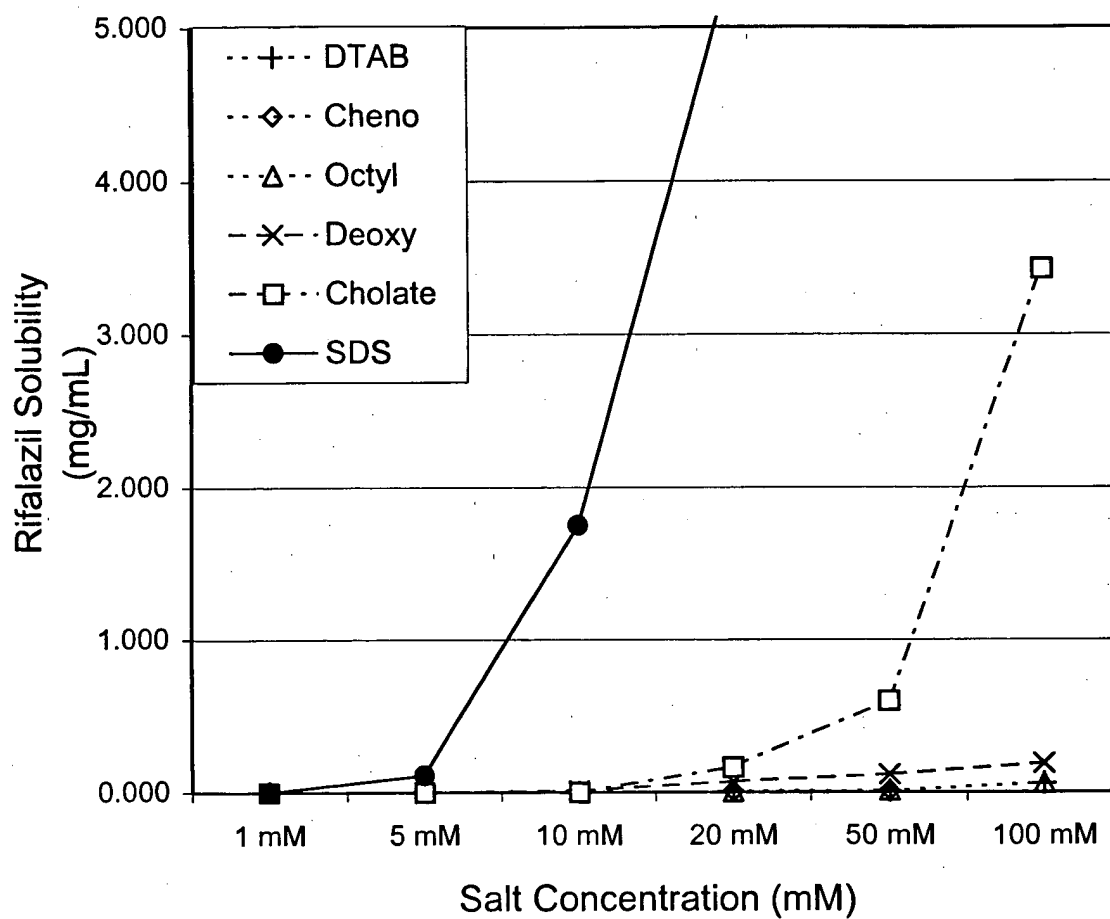


FIG. 5

Effect of SDS on Rifalazil Solubility in Saline at  
Two pHs

